Synthesis and Study Biological Activity of Some New Isoxazoline and Pyrazoline derivatives

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Abstract

This work involves synthesis of novel Schiff bases derivatives contining isoxazoline or pyrazoline units starting with chalcons . 4-Aminoacetophenone was reacted with 3-nitrobenzaldehyde in basic medium giving chalcone [I] by claisen-schemidt reaction. The chalcone [I] was reacted with hydroxylamine hydrochloride giving isoxazoline [II] in basic medium. The chalcone [I] could also react with hydrazitne hydrate to give pyrazoline [III] . The novel Schiff bases with structural formula [IV] and [V] were prepared by the reaction of amino compounds ; isoxazoline [II] and pyrazolines [III] with p-substituted aldehydes or p-subsituted ketones, respectively in dry benzene using drops of glacial acetic acid as a catalyst with reflux. All the synthesized compounds have been characterized by melting points , FTIR and ^{1}HMNR (of some of theme) spectroscopy. The biological activity of all compounds was examined against antibacterial ; gram(+) and gram(-).

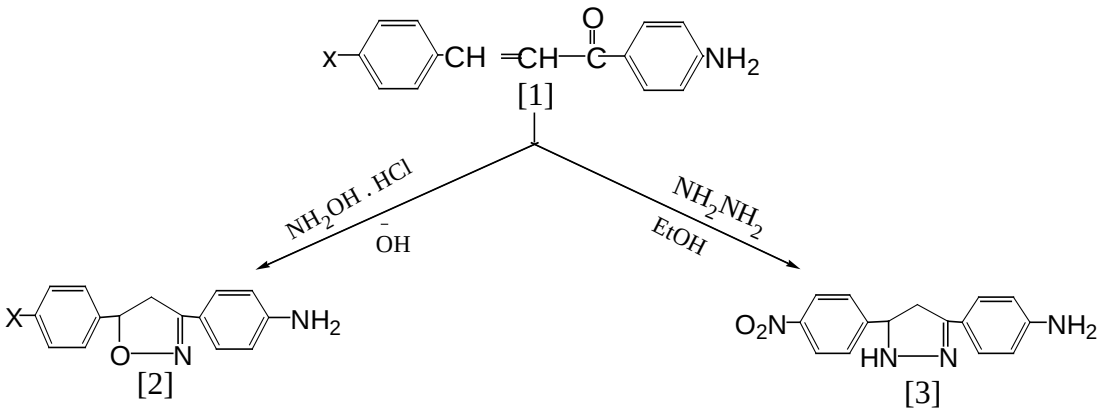
Key words : chalcone , pyrazoline , isoxazoline , Schiff bases

Introduction

Isoxazoline and pyrazolines derivatives have been reported to possess biological activity[1-4] . In addition, isoxazoline derivatives have played a crucial role as intermediates in the organic synthesis of number of heterocyclic pharmacological active compounds[5].

Various methods are used for the preparation of pyrazolines,among these: Treatment of α,β-unsaturated ketones with hydrazines seems to be the most popular procedure for this purpose. This reaction has been conducted under various conditions[6-9].

Isoxazolines (2)and pyrazolines (3) were prepared from the reaction of chalcones [1] with hydroxylamine hydrochloride in NaOH medium or with hydrazine hydrate , respectively [10]



X= NO_2 or Cl

Schiff bases attract much interest both for synthetic and biological point of view [11]. A through literature survey revals that Schiff bases derived from various heterocyclic possess cytotoxic [12] , anticonvulsant [13] , antimicrobial [14] , anticancer [15] , and antifungal [16] activities .

Depending on the above finding , we decided to synthesize A novel Schiff bases containing isoxazoline or pyrazoline units.

Experimental

Materials: All the chemicals were supplied from Merck , GCC and Aldrich Chemicals Co. and used as received .

Techniques : FTIR spectra were recorded using potassium bromide discs on a Shimadzo (Ir prestige-21) FTIR spectrophotometer . ^{1}HNMR spectra were carried out by company : Bruker , model: ultra shield 300 MHz , origin : Switzerland and are reported in ppm(δ), DMSO was used as a solvent with TMS as an internal standard . Measurements were made at chemistry department, Al-albyat university , Uncorrected melting points were determined by using Hot-Stage, Gallen Kamp melting point apparatus.

General procedures

New Schiff bases [IV] and [V] were synthesized according to Scheme 1.

Preparation of (chalcone) 4-[3-(3-nitrophenyl)-2-propene- 1-one]-aniline [I]

Equimolar quantities of 4-amino acetophenone (1.35gm , 0.01mol) and 3-nitrobenzaldehyde (0.01mol) were dissolved in minimum amount of alcohol. Sodium hydroxide solution (0.02 mol) was added slowly and the mixture becomes cold. Then the

mixture was poured slowly into 400mL of ice water with constant stirring and kept in refrigerator for 24 hrs [17] . The glow yellow solid obtained was filtered ,washed and recrystallized from chloroform . yield (86%) , m.p = 198-200 ^{0}C.

Preparation of 4[5-(3ˉ-nitrophenyl)-4,5-dihydroisoxazol-3-yl] aniline [II]

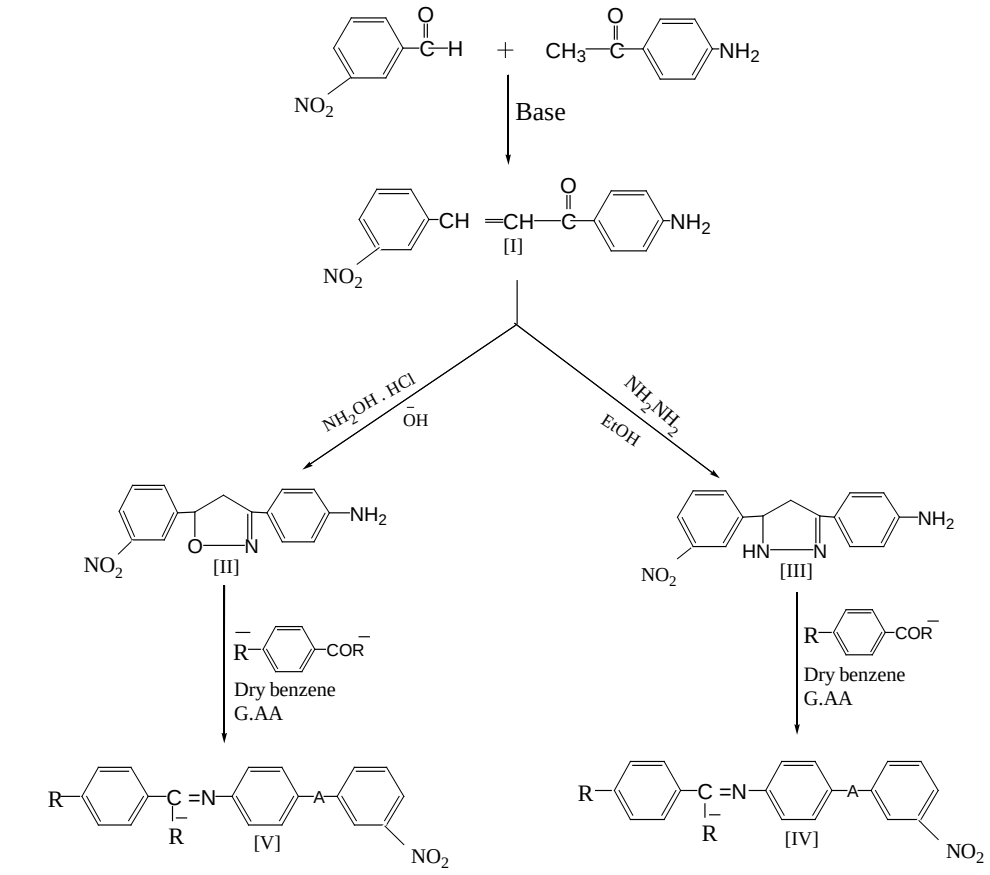
A mixture of chalcone[I] (0.02mol), hydroxylamine hydrochloride (1.39gm , 0.02mol) and sodium hydroxide solution (0.5gm NaOH in 25mL of water) in ethanol (60mL) were refluxed for 6hrs. The mixture was concentrated under vaccum and poured into ice water . The yellow precipitate obtained was filtered , washed and recrystallized from ethanol .yield (65%), m.p = 130-132 ^{0}C.

Preparation of 4[5-(3ˉ-nitrophenyl)-4,5-dihydro-1H-pyrazol -3-yl]-aniline [III]

A mixture of chalcone [I] (0.01mol) and hydrazine hydrate (05gm , 0.01mol) in ethanol (15 mL) was heated under reflux for 6hrs. After cooling the separated orange solid was filtered off, dried and crystallized from ethanol [18] . yield (75%) ,m.p = 140-142 ^{0}C.

Synthesis of Schiff bases

Amixture of new amino compounds [II] or [III] (0.01 mol) ,different aromatic aldehydes or ketones (0.01 mol), dry benzene (15 mL) and 2drops of glacial acetic acid was refluxed for 3hrs . The solvent was evaporated under vaccum and the residue crystallized from chloroform . The physical data of these Schiff bases are listed in Table 1.



Scheme 1

Results and discussion

Chalcone was chosen as the starting material for the synthesis of different heterocyclic compounds , such as : isoxazolines ,pyrazolines derivatives by using approperative reagents for that purpose .

The chalcones [I] is synthesized by claisen-schmidt condensation of 4-amino acetophenone and 3-nitrobenzaldehyde by base catalyzed followed by dehydration to yield the desire chalcones. The structural assignments of the chalcones [I] are based on melting points and FTIR spectroscopy.

The FTIR spectrum indicated the appearance of two bands in the region (3221-3425)cm^{-1} which could be attributed to asymmetric and symmetric stretching vibration of NH_2 group,a week band at 3086cm^{-1} due to stretching vibration of (=C-H) group, two peaks at 1651cm^{-1} and 1632cm^{-1} due to of C=O and C=C (CH=CH) stretching vibrations,respectively.

Isoxazoline compound [II] was synthesized from the reaction of chalcones [I] with hydroxylamine hydrochloride in alkaline medium.

The structure of this compound[II] has been characterized by melting point and FTIR spectroscopy. The FTIR spectra of isoxazoline [II] showed the disappearance of two absorption bands of the CH=CH and C=O group in the starting material [I] together with appearance of new absorption bands for C=N and C-O (cyclic ether) groups around 1610 cm^{-1} and 1178 cm^{-1}, respectively .

The chalcone [I] was further reacted with hydrazine hydrate in ethanol absolute to yield the corresponding pyrazoline derivative.

The structure of the pyrazoline [III] was identified by melting point and FTIR spectroscopy. The FTIR spectrum of this compound showed the disappearce of two absorption bands of the CH=CH and C=O group ,in the chalcone [I] and appearance of new absorption bands of NH and C=N group at 3319cm^{-1} and 1639cm^{-1} ,respectively.

The new Schiff bases [IV] and [V]were synthesized by refluxing aromatic primary amine [II] or [III] and different aromatic aldehydes or aromatic ketones in dry benzene with some drops of glacial acetic acid (GAA).

These Schiff bases were identified by their melting points , FTIR and ^{1}HNMR spectroscopy . FTIR absorption-spectra showed, Figure (1), the disappearance of absorption bands due to NH_2 and C=O groups of the starting materials together with appearance of new absorption band in the region (1680-1643)cm^{-1} which is assigned to C=N stretching.

The other data of functional groups which are characteristic of these compounds are given in Table 2.

^{1}HMNR spectrum of Schiff base $[V]_c$, Figure (2), shows the following signals: twelve aromatic protons appeared in the region δ 7.18-8.74 ppm , sharp singlet at δ 11.85 ppm that could be attributed to azomethine protons . A triplet signal at δ 6.80-6.92 ppm is due to one proton of (CH) pyrazoline ring , six protons triplet at δ 3.12 ppm that are attributed to $2CH_3$ groups . Two protons of CH_2 (pyrazoline) appears as doublet at δ 6.54-6.62 ppm , and a singlet signal at δ 8.74ppm which was assigned to proton of NH group.

Biological Activity

All the newly synthesized compounds were initially screened for their *in vitro* antimicrobial activities against the Gram-positive (*S. aureus*) and the Gram negative (*E. coli, K. Pneumoniae, P.aervginosa and Serratia Spp*) by disc diffusion. The inhibitory effect of these compounds against these micro-organisms is given in Table 3 . The screening results indicate that some of the compounds exhibit the antimicrobial activity. Each compounds was dissolved in DMSO to give concentration 1ppm. The plates were then incubated at 37 ^{0}C and

examined after 24 hrs. The zones of inhibition formed were measured in millimeter and are represented by (-), (+), (+ +) and (+ + +) depending upon the diameter and clarity as in Table 3. Most of the compounds exhibit the high or low biological activity , the biological activities data are listed in Table 3.

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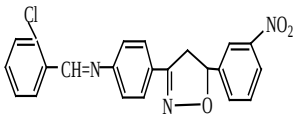
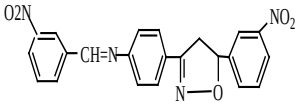
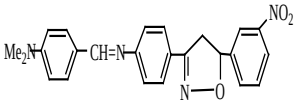
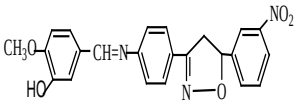
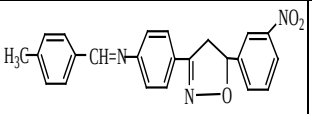
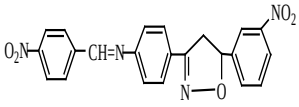
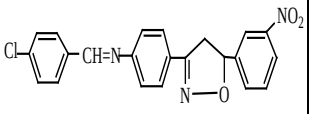
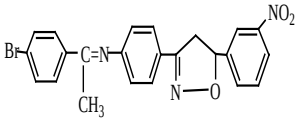
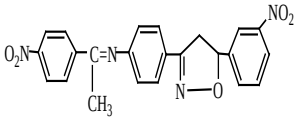
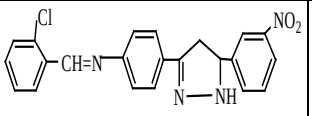
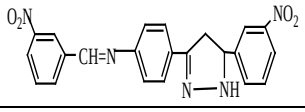
Table (1): Physical properties of Schiff bases [IV] and [V]

comp. No.	Nomencalture	Structural Formula	Molecular Formula	M.P C^0	Yield %	Color
$[IV]_a$	3[2-chloro benzylidene amino phenyl]-5-(3-nitrophenyl)-4,5-dihydroisoxazole		$C_{22}H_{16}N_3O_3Cl$	100-102	65	Pale yellow
$[IV]_b$	3[3-nitro benzylidene amino phenyl]-5-(3-nitrophenyl)-4,5-dihydroisoxazole		$C_{22}H_{16}N_3O_5$	176-178	67	Dark yellow
$[IV]_c$	3[4-N,N-dimethylamino benzylidene amino aniline]-5-(3-nitrophenyl)-4,5-dihydroisoxazole		$C_{24}H_{22}N_4O_3$	154-156	66	Orange
$[IV]_d$	3[4-methoxy-3-hydroxy benzylidene amino phenyl]-5-(3-nitrophenyl)-4,5-dihydro isoxazole		$C_{23}H_{19}N_3O_5$	97-99	70	Yellow
$[IV]_e$	3[4-methyl benzylidene amino phenyl]-5-(3-nitrophenyl)-4,5-dihydroisoxazole		$C_{23}H_{19}N_3O_3$	162-164	58	Orange-yellow
$[IV]_f$	3[4-nitro benzylidene amino phenyl]-5-(3-nitrophenyl)-4,5-dihydroisoxazole		$C_{22}H_{19}N_4O_5$	156-158	66	Pale yellow
$[IV]_g$	3[4-chloro benzylidene amino phenyl]-5-(3-nitrophenyl)-4,5-dihydroisoxazole		$C_{22}H_{16}N_3O_3Cl$	122-124	60	Brown
$[IV]_h$	3[4-bromro isomethyl benzyliden amino phenyl]-5-(3-nitrophenyl)-4,5-dihydroisoxazole		$C_{23}H_{18}N_3O_3Br$	51-53	58	Pale brown
$[IV]_i$	3[4-nitro isomethyl benzylidene amino phenyl]-5-(3-nitrophenyl)-4,5-dihydroisoxazole		$C_{23}H_{18}N_4O_5$	74-76	60	Pale Orange
$[V]_a$	3[2-chloro benzylidene aminophenyl]-5-(3-nitrophenyl)-4,5-dihydro-1H- pyrazole		$C_{22}H_{17}N_4O_2Cl$	118-120	55	Red-brown
$[V]_b$	3[3-nitro benzylidene aminophenyl]-5-(3-nitrophenyl)-4,5-		$C_{22}H_{17}N_5O_4$	150-152	65	Yellow

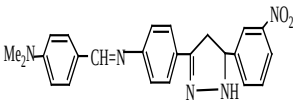
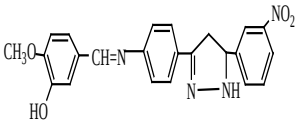
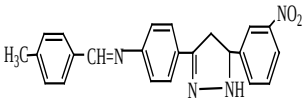
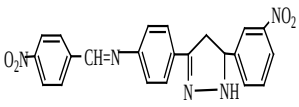
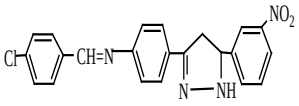
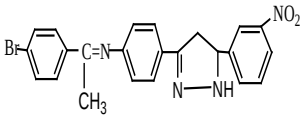
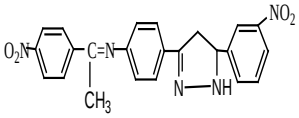
	dihydro-1H- pyrazole					
$[V]_c$	3[4-N,N-dimethyl benzylidene aminoaniline]-5-(3-nitrophenyl)-4,5-dihydro-1H- pyrazole		$C_{24}H_{23}N_5O_2$	158-160	58	Red
$[V]_d$	3[4-methoxy-3-hydroxy-benzylidene aminophenyl]-5-(3-nitrophenyl)-4,5-dihydro-1H- pyrazole		$C_{23}H_{20}N_4O_4$	108-110	60	Brown
$[V]_e$	3[4-methyl benzylidene aminophenyl]-5-(3-nitrophenyl)-4,5-dihydro-1H- pyrazole		$C_{23}H_{20}N_4O_2$	180-182	55	Orange
$[V]_f$	3[4-nitro benzylidene aminophenyl]-5-(3-nitrophenyl)-4,5-dihydro-1H- pyrazole		$C_{22}H_{17}N_5O_4$	100-102	65	Red-orange
$[V]_g$	3[4-chloro benzylidene aminophenyl]-5-(3-nitrophenyl)-4,5-dihydro-1H- pyrazole		$C_{22}H_{17}N_4O_2Cl$	122-124	58	Brown
$[V]_h$	3[4-bromo isomethyl benzylidene aminophenyl]-5-(3-nitrophenyl)-4,5-dihydro-1H- pyrazole		$C_{23}H_{19}N_4O_2Br$	200-202	50	brown
$[V]_i$	3[4-nitro isomethyl benzylidene aminophenyl]-5-(3-nitrophenyl)-4,5-dihydro-1H- pyrazole		$C_{23}H_{19}N_5O_4$	140-142	55	Orange-red

Table (2): Characteristic FTIR absorption bands of Schiff bases [IV] and [V]

Comp. No.	νNH	νC-H aliph	νC=N exocyc.	νC=N endocyc.	νC=C aromatic	others
$[IV]_a$		2922-2856	1680	1607	1595	2-Cl:820
$[IV]_b$		2878	1660	1613	1586	$3NO_2$:1504, 1352
$[IV]_c$		2857-2824	1647	1609	1584	4-$N(Me)_2$: 1346
$[IV]_d$		2890-2837	1690	1620	1592	4-OH:3430
$[IV]_e$		2915-2850	1650	1608	1595	
$[IV]_f$		2866	1660	1607	1586	4-NO_2:1508, 1321
$[IV]_g$		2922-2857	1657	1607	1590	4-Cl:822
$[IV]_h$		2860-2820	1645	1615	1584	Br : 675
$[IV]_i$		2924-2855	1681	1615	1595	4-NO_2:1508,1319
$[V]_a$	3379	2918-2847	1657	1610	1597	2-Cl:806
$[V]_b$	3383	2910-2868	1661	1620	1595	$3NO_2$:1525, 1320
$[V]_c$	3402	2922-2855	1659	1615	1597	4-$N(Me)_2$: 1313
$[V]_d$	3361	2935-2820	1665	1620	1590	4-OH:3220
$[V]_e$	3360	2920-2851	1693	1607	1595	
$[V]_f$	3393	2926-2853	1680	1625	1597	4-NO_2:1521, 1319
$[V]_g$	3390	2924-2855	1660	1624	1593	4-Cl:827
$[V]_h$	3390	2903-2830	1653	1624	1597	Br : 678
$[V]_i$	3344	2960-2825	1643	1609	1580	4-NO_2:1528,1300

Table (3) : antibacterial activity of the synthesized compounds [II]-[V]

Comp. No.	Klebsiella Pneumoniae(G-)	Pseudomonas aervginosa (G-)	Serratia Spp. (G-)	E.Coli(G-)	Staphlococcus aurus (G+)
[II]	+	+ +	+	+ +	+ + +
[III]	+	+	+	+	+
$[IV]_a$	+	+ + +	+ + +	+ + +	+ + +
$[IV]_b$	+	+ +	+ +	+ +	+ +
$[IV]_c$	+ +	+	+ +	+	+ +
$[IV]_d$	-	-	-	+	-
$[IV]_e$	+	-	+	+	+
$[IV]_f$	+	+	+	+	+
$[IV]_g$	+	-	+	+	+
$[IV]_h$	+	+ + +	+ + +	+ + +	+ + +
$[IV]_i$	+ +	+ +	+ + +	+ +	+ + +
$[V]_a$	+	-	+	+	+
$[V]_b$	+	+	+	+	+
$[V]_c$	+ +	+ +	+ +	+ +	+ +
$[V]_d$	-	-	-	+	-
$[V]_e$	+ + +	+ + +	+ + +	+ + +	+ + +
$[V]_f$	+	+	+ +	+	+ +
$[V]_g$	+	-	+	+	+
$[V]_h$	+	+	+ +	+	+ +
$[V]_i$	+ +	+	+ +	+ + +	+ +

Key to symbols: Highly active = + + +(mor than)15 mm.
Moderately active = + +(11-15) mm and slightly active = + (5-10) .

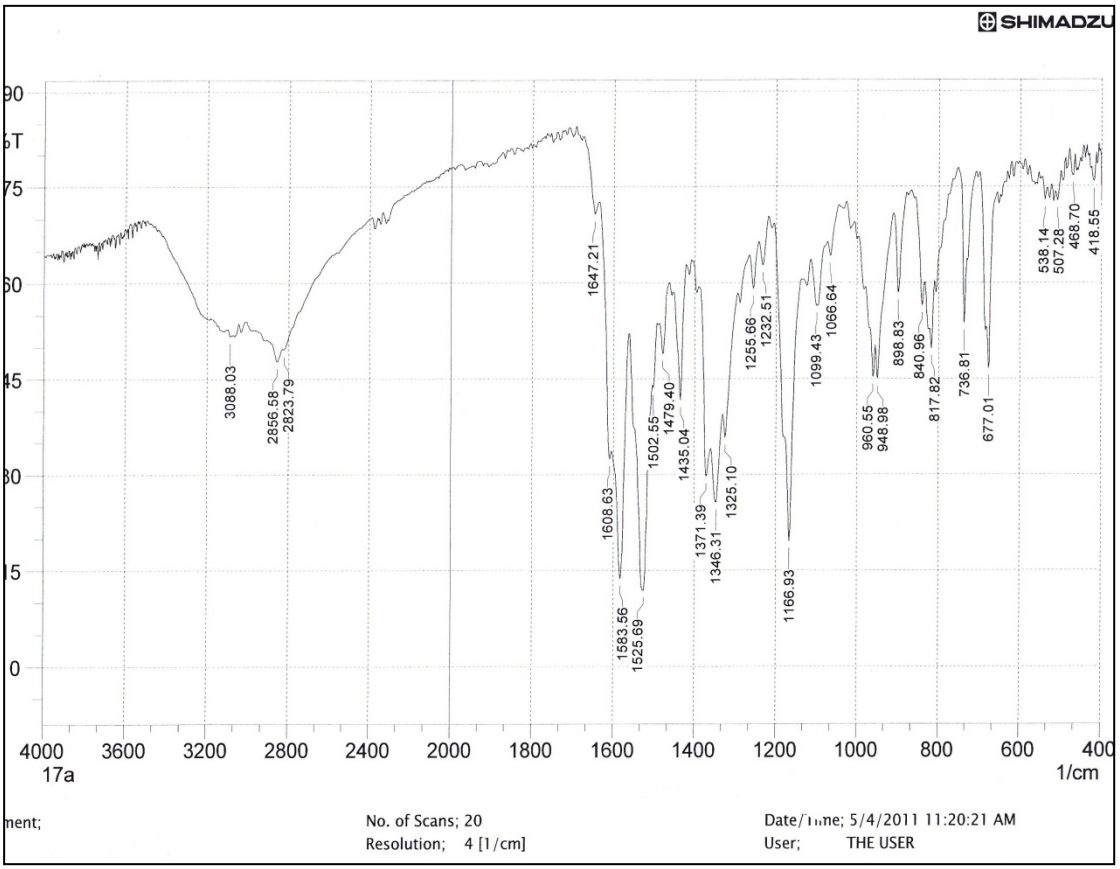


Fig. (1) :FTIR- spectrum of compound $[IV]_c$

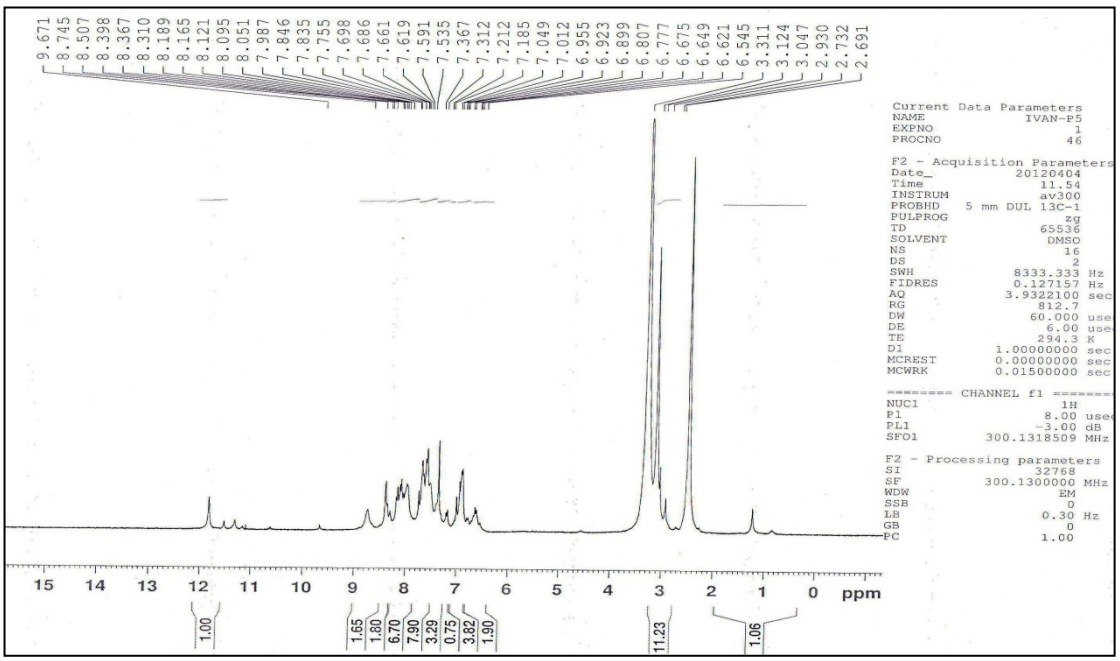


Fig. (2):^{1}HNMR spectrum of compound $[V]_c$

تحضير ودراسة السلوك البايولوجي لبعض مشتقات الاوكزازولين والبايرازولين الجديدة

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الخلاصة

يتضمن هذا البحث تحضير قواعد شف جديدة تحتوي على حلقات غير متجانسة متنوعة مثل أوكزازولين ، بايرازولين باستعمال الجالكون مادة اساسية ، يحضر الجالكون [I] من تفاعل4 -أمينو اسيتوفينون مع 3-نايتروبنزالديهايد في وسط قاعدي بوساطة تفاعل كلايسين-شمدت. يتفاعل الجالكون [I] مع هايدروكسيل أمين هايدروكلورايد في وسط قاعدي مؤديا الى تكوين مشتقات الايزوكزازولين [II] ، بينما يؤدي تفاعل أحد أ نواع الجالكونات [I] مع الهايدرازين الى تكوين البايرازولين [III]. حضرت قواعد شف [IV] و [V] من تفاعل مركبات حلقية غير متجانسة مختلفة ؛ أوكزازولين [II] اوالبايرازولين [III] مع ألديهايدات او كيتونات متنوعة على التوالي في بنزين جاف وقطرات من حامض الخليك الثلجي مع التصعيد العكسي.
شخصت جميع المركبات المحضرة في هذا البحث من خلال قياس درجات أنصهارها فضلا عن الطرائق الطيفية المتمثلة بطيف الأشعة تحت الحمراء وطيف الرنين النووي المغناطيسي البروتوني (للبعض منها). كما درست الفعالية البايولوجية لجميع المركبات المحضرة ضد انواع من البكتريا هي كرام (+) وكرام (-).

الكلمات المفتاحية : الجالكون ، الاوكزازولين ، البايرازولين ، قواعد شف